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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,097	03/15/2004	Gustavo Antonio Moviglia	545872000100	4725

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
07/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/802,097	MOVIGLIA, GUSTAVO ANTONIO	
	Examiner	Art Unit	
	SANDRA WEGERT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 24-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The examiner in charge of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Sandra Wegert in Group Art Unit 1647.

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

Applicants Arguments/Remarks, sent 1 May 2009, have been entered. Claims 1-77 are pending in the instant application. Claims 1-9 and 24-77 are withdrawn. Claims 10-23 are currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, Science, 263: 518-520, of record 03/15/2004), in view of Moviglia, G.A. (1996, Transfus. Sci., 17(4): 643-649, of record 03/15/2004).

Guo et al. teach fusion of rat hepatocellular carcinoma cells with activated B-cells, producing tumor/B-cell hybrids (TBH) that have lost their tumorigenicity and immunogenicity (see abstract). Guo et al teach that the TBH injection eradicated established hepatomas in 5 out of six rats, and also prolonged group survival as a whole (p. 519, Figure 2). Furthermore, Guo et al teach that CD8+ cells can mediate tumor cell destruction in the absence of CD4+ cells, and such action is tumor-specific (see page 519 Table 1 and page 520, 1st paragraph). In addition, the researchers showed that pre-immunization with the hepatocellular-specific TBH cells prevented tumor formation in rats that were subsequently injected with hepatocellular tumor cells (p. 520, 2nd paragraph). Lastly, Guo et al teach that the successful production and use of such a tumor/B-cell hybrid, and its successful use in treating cancer, has broad clinical applications and may provide a useful strategy for cancer immunotherapy (p. 520, last paragraph).

Guo et al. does not teach a *composition* comprising a plurality of cells including isolated human CD8+ cells and tumor/B-cell hybrid cells (i.e., their vaccine did not include CD8+ cells).

Moviglia, et al, teach that patients injected with tumor/B-cell hybrid cells show that TBH auto-vaccination has a positive therapeutic effect on different human tumors, especially breast tumors, and does so with low overall toxicity. Moviglia also teaches that the activated B-cell is one of the best antigen-presenting cell (APC) for both CD4 and CD8 cells because the lymphocyte is able to express not only MHC II molecules on its membrane, but every other

necessary co-stimulating compound as well. Through the hybridization procedures, these B-cell properties are transmitted to the tumor cells, allowing a rigorous response by the immune system in attacking the tumor (p. 647, last paragraph of 1st column., through 1st paragraph of 2nd column). Moviglia indicated that the anti-tumor effect of TBH in the induction period needs both CD4 and CD8 cells, provided that their number is sufficient and their competence normal, whereas in the progression and maintenance stage of the cancer, only CD8 cells are necessary.

It would have been obvious to one of ordinary skill in the art to make a composition comprising isolated CD8+ cells and TBH cells from the same individual based on the combined teaching of Guo et al. and Moviglia. One of ordinary skill in the art would be motivated to do so because of the observation of Guo et al that the CD8+ cells activated by the TBH are involved in tumor rejection. The ordinary artisan would therefore want to have more activated CD8+ cells available for the killing of tumor cells in the host, especially when the host does not have sufficiently competent CD8+ cells, because, as discussed by Guo, tumors developed only in rats that had depleted CD8+ cells populations (p. 519, middle column). In addition, the level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill in the art would have a reasonable expectation of success of activating CD8+ cells either in vitro or in vivo, and then combining them in a composition with TBH cells. Therefore, the claimed invention would have been prima facie obvious at the time the invention was made.

Claims 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, Science, 263: 518-520), in view of Moviglia (1996, Transfus. Sci., 17(4): 643-649) and Gong et al (WO 01/59073).

The teaching of Guo and Moviglia have been discussed above. Guo and Moviglia do not teach a *method* of generating CD8+ cells that had been activated by contacting the isolated CD8 cells with tumor/B-cell hybrid cells for a sufficient time to stimulate proliferation of CD8+ cells that recognize tumor antigens.

Gong et al. teach a method of activating T-cells by contacting CD8+ T-cells with tumor antigen-fused cells both in vitro and in vivo (see for example, page 13, lines 10-32, page 25, lines 23-29, and page 27, 2nd and 3rd paragraphs). The obviousness of generating a composition comprising isolated TBH cells combined with CD8+ cells were discussed above. The method of generating said CD8+ cells is documented in the prior art as evidenced by Gong et al. In addition, Gong et al. teach the method of generating activated CD8+ cells by contacting said cells with the appropriate antigen either in vivo or in vitro. The person of ordinary skill in the art would have been motivated to create such cells, because as disclosed in Guo et al in view of Moviglia, CD8+ cells are necessary for the anti-cancer effect of the tumor/B-cell hybrid. Absent evidence from the contrary, one of ordinary skill in the art would have a reasonable expectation of success of activating CD8+ cells as claimed. Furthermore, to test whether such cells would have an anti-tumor effect in vivo, it would have been obvious to inject the composition into an individual. For these reasons, the claimed invention would have been prima facie obvious at the time the invention was made.

Applicants argue that the examiner has not adequately provided a rationale for why "the unpredictability with regard to the claimed composition can be ignored" (Remarks, 1 May 2009,

p. 2, 3rd paragraph), and show that in fact, the examiner emphasized therapeutic activity in the Obviousness rejection under 35 U.S.C. § 103(a) (Remarks, p. 2, 4th paragraph).

Applicant's arguments filed 1 May 2009 have been fully considered but they are not persuasive for the following reasons:

The examiner was no doubt referring to the fact that it is obvious to make small improvements in a system if there is a potential for better treatment with the improved invention (Office action, 4 April 2008, p. 5 lines 11-16). In other words, "[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it" (KSR, 550 U.S., 82 USPQ2d at 1391, as cited in MPEP 2141, § II, 3rd paragraph). The examiner was also attempting to refute Applicants' arguments that the Guo system is a "failed system" (Applicants' Remarks, 12 December 2007, p. 4, last paragraph), which it clearly is not, as explained in the 35 U.S.C. § 103(a) Obviousness rejection (above).

Applicants also discuss the guidelines that must be followed when determining Obviousness under 35 U.S.C. § 103(a), which the examiner agrees with (Remarks, 1 May 2009). For example, the applicants discuss that the motivations to combine sources come from the following rationales:

"(A) Combining prior art elements according to known methods to *yield predictable results;*

(B) Simple substitution of one known element for another to obtain *predictable results;*

(C) Use of *known technique* to improve *similar devices* (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to *yield predictable results;*

(E)"Obvious to try" - choosing from a finite number of identified, predictable solutions, with *a reasonable expectation of success;*

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are *predictable* to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention." (Remarks, 1 May 2009, p. 3, applicants' italics).

Applicants then argue that none of these rationales (A-G) applies to the instant case.

Applicant's arguments have been fully considered but are not persuasive for the following reasons:

The rejections under 35 U.S.C. § 103(a) (above) provide valid rationales for combining the references discussed. Guo, et al, conceived of the idea of a tumor vaccine, produced a tumor/B-cell hybrid and "vaccinated" rats against a cancer. In that case, the result of additionally adding CD8+ cells to an already successful vaccine would be predicted to make the vaccine more effective, since Guo, et al discussed the importance of CD8 cells in the vaccination process (similar to rationale (A) above). Guo, et al, also "cured" (their term) cancer in rats that already had progressive cancer with this method. The techniques used to combine elements were known (rationale (C)) and the results are predictable (rationale (D)). In addition, as discussed above, it would be obvious to try to improve a treatment, and as such one would have a reasonable chance of success (rational (E)). Guo, et al discussed *at length* the importance of activated CD8+ cells in the body's response to the tumor/B-cell hybrid cells, and that the extent of the cancer was related to CD8 cell presence and competence. Guo, et al even provided data comparing cancer treatments in rats with normal CD8 cells versus rats with depleted CD8 cells (Table 1). As such,

Guo et al provided "teaching, suggestion and motivation" (rationale (G)) to modify the vaccine comprising the tumor/B-cell hybrid cells by adding CD8+ cells to it in order to get a greater response of the immune system when responding to cancer

Conclusion

No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you

would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

/SLW/
26 June 2009

/Manjunath N. Rao /
Supervisory Patent Examiner, Art Unit 1647